

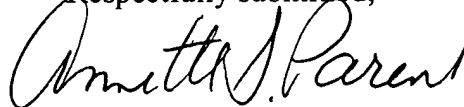
Applicants request entry of this amendment in adherence with 37 C.F.R. §§1.821 to 1.825. This amendment is accompanied by a floppy disk containing the above named sequences, SEQ ID NOS:1-12, in computer readable form, and a paper copy of the sequence information which has been printed from the floppy disk.

The information contained in the computer readable disk was prepared through the use of the software program "PatentIn" and is identical to that of the paper copy. This amendment contains no new matter.

Attached hereto is a marked-up version of the changes made to the Specification by the current Amendment. The attached pages are captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Paragraph beginning at line 32 of page 2 has been amended as follows:

Fig. 2 is a chart showing the alignment of predicted Rbx1 protein sequences from human (SEQ ID NO:1), mouse (SEQ ID NO:1), *Drosophila melanogaster* (SEQ ID NO:6) ~~*Drosophila melanogaster*~~, *Caenorhabditis elegans* (SEQ ID NO:7) ~~*Caenorhabditis elegans*~~, and *Saccharomyces cerevisiae* (SEQ ID NO:2) ~~*Saccharomyces cerevisiae*~~ with APC11 from *S. cerevisiae* (SEQ ID NOS:8 and 9) ~~*S. cerevisiae*~~, wherein DROS = ~~*Drosophila melanogaster*~~ *Drosophila melanogaster*; ELEGANS = ~~*Caenorhabditis elegans*~~ *Caenorhabditis elegans*; and YEAST = *Saccharomyces cerevisiae* ~~*Saccharomyces cerevisiae*~~. The alignment was generated using the MACAW program. (Schuler, *et al.* 1991. "A workbench for multiple alignment construction and analysis," *Proteins; Struct Funct Genet* 9:180-190). Dark shading indicates positions of identity between Rbx1 proteins from different species and positions of identity between the Rbx1 and APC11 proteins. Grey shading indicates positions ~~position~~ of similarity.

Paragraph beginning at line 13 of page 9 has been amended as follows:

The VHL tumor suppressor complex was fractionated by 13% SDS-polyacrylamide gel electrophoresis. Proteins were visualized by staining with Coomassie blue, excised, and subjected to in-gel reduction, S-carboxyamidomethylation, and tryptic digestion. Using 10% of the digestion mixture, peptide sequences were determined in a single run by microcapillary reversed-phase chromatography coupled to the electrospray ionization source of a quadrupole ion trap mass spectrometer (Finnigan LCQ). The ion trap's online data-dependent scans allowed the automatic acquisition of high resolution

spectra to determine charge state and exact mass, and tandem mass spectrometry spectra for sequence information. The relative collision energy was 35% AND ISOLATION WIDTH WAS 2.5 Dalton. Searches of the EST database performed using TLASTIN algorithm identified human and mouse ESTs that encoded the peptide sequences NHIMDLCIECQAN (SEQ ID NO:10), QVCPLDNREWEFQK (SEQ ID NO:11), WNAVAL (SEQ ID NO:12) and WLK which were determined by ion trap mass spectrometry of the 16 kDa polypeptide that copurified with the VHL complex. The identification was facilitated with the algorithm SEQUEST (Eng, *et al.* 1994. *J Am Soc Mass Spectrom* 5:976) and by programs developed in the Harvard Microchemistry Facility (Chittum *et al.* 1998. *Biochemistry* 37:10866). I.M.A.G.E. Consortium cDNA colonies ("I.M.A.G.E. Consortium: an integrated molecular analysis of genomes and their expression," *Genomics* 33:151-152) encoding the complete 108 amino acid long ORFs of human (H71993) and mouse (W66989 and AA260889) Rbx1 were obtained from Research Genetics, Huntsville, Alabama, and the nucleotide sequences of both strands were determined. Human and mouse cDNAs encoded identical polypeptides of 108 amino acids. The amino acid sequence for human and mouse Rbx1 is shown in Fig. 2 and in SEQ ID NO:1. The nucleotide sequence for the human Rbx1 DNA is shown in nucleotides 7-333 or SEQ ID NO:3 and the nucleotide sequence for the murine Rbx1 DNA is shown in nucleotides 18-344 or SEQ ID NO:5, inclusive of the stop codon. Nucleotides 1-6 and 1017 are 5' untranslated regions, respectively and 334-508 and 345-504 are 3' untranslated regions, respectively.